

specification. Claims 1, 8, 13 and 18 have been amended to refer to particular amino acids of SEQ ID NOS: 12 and 15 in accordance with the Examiner's suggestion.

Objection to Claims 1, 8, 13 and 18 under 37 C.F.R. § 1.821(d)

Claims 1, 8, 13 and 18 are objected to under 37 C.F.R. § 1.821(d) for failing to recite the SEQ ID NOS. The Examiner notes that Claims 1, 8, 13 and 18 have been amended to recite portions of SEQ ID NOS: 12 and 15. The Examiner states that "sequences recited in the claims must be identified" and suggests amending the claims to recite the amino acids referred to in SEQ ID NOS: 12 and 15 or assign SEQ ID NOS to the particular portions claimed.

Claims 1, 8, 13 and 18 have been amended to refer to particular amino acids of SEQ ID NOS: 12 and 15.

Objection to the specification under 37 C.F.R. § 1.821(d)

The specification is objected to under 37 C.F.R. § 1.821(d) "for failing to disclose SEQ ID Nos. for the CDRs in the brief descriptions for Figures 7 and 9" (Office Action, page 3).

The brief descriptions of Figures 7 and 9 in the specification have been amended to refer to particular amino acids of SEQ ID NOS: 12 and 15 as suggested by the Examiner.

Rejection of Claims 1-9, 11-15, 18-20, 23, 24, 27 and 28 under 35 U.S.C. §103(a)

The rejection of Claims 1-9, 11-15, 18-20, 23, 24, 27 and 28 under 35 U.S.C. §103(a) as being unpatentable over Queen *et al.* (U.S. Patent No. 5,530,101) in view of Lazarovits *et al.* (*J. Immunol.*, 151(11):6482-6489 (1993)) is maintained for the reasons set forth in the previous Office Action.

In response to Applicants' argument that there is no suggestion to combine the cited references, the Examiner notes that the teaching, suggestion or motivation to combine or modify the teachings of the prior art can be found in either the references themselves or in the knowledge generally available to one of ordinary skill in the art. The Examiner states that "it was well known in the art to use antibodies directed to adhesion molecules or their respective ligands to treat inflammation by preventing the adhesion molecule - ligand interaction" and that "[b]ecause a goal of clinical medicine is to treat human patients, it would have been obvious to make a therapeutic reagent that would have a reasonable expectation of success in humans" (Office Action, page 4). The Examiner further states that Queen *et al.* teach "three potential advantages

over mouse or in some cases chimeric antibodies for use in human therapy" and that "humanized Igs can be more economically produced" (Office Action, page 4). The Examiner cites Lazarovits *et al.* as teaching 1) the Act-1 mAb; 2) that the antigen recognized by Act-1 is $\alpha 4\beta 7$, the receptor for fibronectin and vascular cell adhesion molecule-1; and 3) that $\alpha 4\beta 7$ "may" be beneficial in the immunotherapy of rheumatoid arthritis (RA). It is the Examiner's opinion that based on the teachings in the Lazarovits *et al.* reference "it is reasonable to assume that the expression of the adhesion molecule, $\alpha 4\beta 7$, is important, for example, in rheumatoid arthritis" and that:

[g]iven knowledge in the art of success of antibodies specific for adhesion molecules acting as antagonists and inhibiting inflammation *in vivo*, one of ordinary skill in the art would have been motivated to generate a humanized anti- $\alpha 4\beta 7$ antibody (Office Action, page 5).

Applicants respectfully disagree. Applicants' claimed invention is directed to a humanized immunoglobulin having binding specificity for $\alpha 4\beta 7$ integrin which comprises an antigen binding region of nonhuman origin and at least a portion of human origin, wherein the antigen binding region comprises at least one of three CDRs of a light chain variable region and at least one of three CDRs of a heavy chain variable region, the CDRs being defined by novel amino acid sequences determined by Applicants. In view of the absence of a teaching in the art with reference to a particular DNA and/or amino acid sequence of the variable region of the Act-1 antibody, Applicants' invention is not obvious.

Lazarovits *et al.* investigated the expression of $\alpha 4\beta 7$ using the murine Act-1 antibody and concluded that it is "possible that interference with $\alpha 4\beta 7$ may be beneficial in the immunotherapy of RA" (Lazarovits *et al.*, page 6487, column 1), but do not suggest use of the Act-1 antibody for such a purpose. Queen *et al.* describe particular humanized antibodies and humanized heavy and light chains, and a general process for humanization of antibodies. As indicated in the Amendment mailed to the Patent Office on December 8, 1997, the Examiner has provided no evidence which directs the skilled person to select Act-1 antibody for humanization. However, even if the Examiner did provide such evidence, it would, at most, amount to an invitation to try humanizing the Act-1 antibody, which is not a proper basis for a *prima facie* case of obviousness.

The court has clearly stated that:

A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out (In re Deuel, 34 U.S.P.Q.2d 1210, 1216 (U.S. Ct. App. 1995)).

In order to humanize a particular nonhuman antibody it is necessary to isolate and clone the variable region of the nonhuman antibody. The sequence of the variable region of the Act-1 antibody was not known prior to Applicants' invention. In the Bell and Deuel cases the court found Appellants' claimed DNA sequences unobvious in light of prior art teaching a general method of isolating DNA in combination with prior art teaching all or a portion of the amino acid sequences encoded by the claimed DNA sequences (In re Bell, 26 U.S.P.Q.2d 1529 (C.A.F.C. 1993); In re Deuel, 34 U.S.P.Q.2d 1210 (U.S. Ct. App. 1995)). In the present case, the obviousness rejection is based on a prior art teaching of a general method of humanizing a nonhuman antibody, but there is no art teaching the sequence of the variable region of the Act-1 antibody. Based on the holdings in the Bell and Deuel cases, Applicants do not understand how the Examiner can find obvious Applicants' claimed humanized Act-1 antibody in light of prior art which teaches a general method for humanizing antibodies, but does not teach the sequence of the variable region of the Act-1 antibody.

In response to Applicants' argument that there is no teaching of the Act-1 antibody CDR sequences, the Examiner states that:

[w]hether or not Queen *et al.* teach the sequence and humanizing of Act-1 in particular is irrelevant to their having anticipated the CDR-grafted Act-1 of the instant application (Office Action, page 5).

It is the Examiner's opinion that:

[i]t would have been obvious to one of ordinary skill in the art to use Queen's method of producing humanized antibody and art-known techniques of molecular cloning to make humanized antibodies specific for $\alpha 4\beta 7$. Queen *et al.* teach that once an antibody (nonhuman) is chosen, following their criteria, *i.e.*, choosing the human framework, choosing which particular amino acids should be donor or acceptor, and following their reasoning for making changes, any antibody can be humanized. (Office Action, page 6).

Applicants strongly disagree that the lack of teaching of the CDR sequences of the Act-1 antibody in the cited art is not relevant. As pointed out above, the art does not contain a teaching directing a person of skill in the art to choose the Act-1 (nonhuman) antibody for humanization. Furthermore, even if the art did contain such a teaching, the humanized antibody could not be

made without the sequence of the variable region of the Act-1 antibody. That is, choosing the human framework, choosing which particular amino acids should be donor or acceptor and following the reasoning in Queen *et al.* for making changes cannot be performed until the variable region of the nonhuman antibody has been isolated and cloned. The court has clearly stated that:

[t]he fact that one can conceive a general process in advance for preparing an *undefined* compound does not mean that a claimed *specific* compound was precisely envisioned and therefore obvious (In re Deuel, 34 U.S.P.Q.2d 1210, 1216 (U.S. Ct. App. 1995)).

As to the Examiner's reliance on "art-known techniques of molecular cloning" to establish obviousness, the Deuel court, reaffirming the principle stated in Bell, states that:

the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs (*Id.* at 1215).

The Examiner has cited no art that suggest Applicants' claimed sequences. The Examiner's reliance on "art-known techniques of molecular cloning" and a general process for preparing an undefined humanized antibody to support the obviousness rejection of Applicants' claimed humanized Act-1 antibody, for which the sequence of the variable region of the Act-1 antibody was unknown prior to Applicants' disclosure, directly contradicts established case law. The rejection is legally improper.

As stated in the Amendment mailed to the Patent Office on December 8, 1997, the cited references do not teach the CDR sequences recited in the claims or the full sequence of the light and heavy chain variable regions of the Act-1 antibody. As claimed, the invention as a whole is not obvious over the prior art of record, which neither teaches or suggests that the skilled person select Act-1 in particular, neither teaches nor suggests the sequences of the light chain, the heavy chain or the six CDRs of Act-1, and neither teaches nor suggests humanized antibodies having the particular structure claimed.

Withdrawal of the obviousness rejection is respectfully requested.

Fourth Supplemental Information Disclosure Statement (IDS)

Applicants direct the Examiner's attention to the Fourth Supplemental IDS being filed concurrently.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Anne J. Collins
Anne J. Collins
Registration No. 40,564
Telephone (781) 861-6240
Facsimile (781) 861-9540

Lexington, Massachusetts 02421-4799

Dated: March 15, 1999